REMARKS

Reconsideration of the above referenced application is respectfully requested. Upon entry of the foregoing amendment, Claims 1, 3-6, 10-22 and 25-26 are presently pending. Claims 3 and 10-13 have been withdrawn. Claims 1, 14 and 25 have been amended and claims 2, 7-9, 23 and 24 have been cancelled. Basis for the amendments may be found throughout the specification, and in the claims as originally filed. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more continuation or divisional application. No new matter has been introduced and entry of the amendment is requested.

Elections/Restriction

Applicants have amended Claim 1 to reflect scope consistent with the election of the following species: a replication-competent adenovirus vector comprising an E2F-responsive TRE, operatively linked to an E1a coding region.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claim 4 stands rejected under 35 U.S.C. § 112 as having insufficient antecedent basis for the limitation "tumor-specific replication-competent adenovirus vector", because Claim 1 as filed did not have that limitation. Claim 1 has been amended to encompass a "tumor-specific replication-competent adenovirus vector", rendering the rejection moot.

Claim 14 and 15 stand rejected under 35 U.S.C. § 112 as allegedly being vague and indefinite in that they fail to define the structure of the claimed vector, in particular the second gene comprised by the claimed Hela S3 cell.

It is respectfully submitted that the claims as filed are clear and unambiguous. Claim 14 does define the structure of the second gene, requiring that the "second gene" is "essential for replication of said vector". Applicants have amended claim 14 to indicate that the "second gene" "essential for replication of said vector" is an adenovirus gene. The term "gene essential for replication" is defined on p. 8, lines 26-29 and specific examples of genes essential for replication are provided, e.g., E1a, E1b, E2a, E2b and E4 genes. Thus, one skilled in the art would understand that the second gene is a gene essential for replication and, therefore, neither Claim 14 nor Claim 15 is vague and indefinite.

Claim 16 stands rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite in that the claim fails to define where the heterologous gene is inserted into the claimed vector.

The specification at p. 13, line 31 to p. 14, line 2 describes insertion of a heterologous coding sequence, e.g., a therapeutic gene, into the replication-competent adenoviral vectors of the present invention. For instance, it states that the therapeutic gene may be inserted in any position that does not adversely affect the infectivity or replication of the virus and describes preferred locations for inserting the therapeutic gene, e.g., inserted in the E3 region in place of one of the E3 proteins. Thus, in view of the disclosure, one skill in the art would understand the meaning of Claim 16. Hence, Claim 16 is not vague and indefinite and the rejection under 35 U.S.C. §112 second paragraph should be withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-2, 4-9, 14-19 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

Bai et al., J Virol. 68(9):5925-32, 1994, (copy provided herewith as Exhibit 1), demonstrates that wild type Ad2 (Subgroup C including Ad1, 2, 5 and 6) and Ad12 (Subgroup D including) are capable of infecting HeLa cells. The specification demonstrates the successful replication of Ad5-based (Subgroup C) and Ad35-based (Subgroup B including Ad3 Ad7, and Ad11) replication-competent adenoviral vectors in HeLa-S3. Therefore, at least three different Ad Subgroups have been shown to be able to infect Hela cells. Furthermore, Segerman et al., Journal of Virology, Vol. 77(17): 9183-9191, 2003, (copy provided herewith as Exhibt 2), demonstrates that Subgroup B adenoviruses (e.g., Ad3, Ad7 and Ad35) use CD46 as the receptor, which is expressed on all nucleated cells. In addition, Wu et al., J. Virol., 78(8) 3897-3905, 2004, have demonstrated that Subgroup D adenoviruses (e.g., Ad8, Ad19, and Ad37), also use CD46 as a receptor.

It follows that the knowledge generally available to those of skill in the art taken together with the disclosure of the specification provides detailed guidance on how to make and use the claimed invention. The specification demonstrates successful infection and replication in Hela-S3 cells, e.g., harvesting virus (Example 4), quantification of virus (Example 5), and production of oncolytic viruses in HeLa-S3 cells (Examples 7 & 8).

Accordingly, it would not require undue experimentation for one skilled in the art to determine whether any given adenoviral vector was replication competent in HeLa-S3 cells and the rejection under 35 U.S.C. § 112, first paragraph, should therefore be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-2 and 18 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Bai et al. (J. Virol. 1994, Vol. 68, No. 9, pp. 5925-5932) in view of the disclosures of Stanziale et al. Current Molecular Medicine Feb. 2003, Vol. 3, pp. 61-71, especially pages 64-66) and Turturro et al (Blood, 1998, Vol. 92,, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640), for the reasons set forth on page 6 of the Office Action.

For anticipation to lie under 35 U.S.C. § 102, a reference "must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present." (MPEP §706.02). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Bai et al. is cited as disclosing Hela-S3 cells comprising wild type adenovirus, which is considered to be oncolytic in view of the disclosure of Stanziale et al. and is considered to support tumor-specific adenovirus replication in view of the disclosure of Turturro et al. Turturro et al. is cited as teaching that Hela S3 cells express high levels of CAR which make them susceptible to infection by adenovirus.

None of Bai et al., Stanziale et al., or Turturro et al. disclose a recombinant tissue-specific or tumor-specific replication competent adenoviral vectors comprising the E2F promoter operatively linked to an E1a coding region, as presently claimed.

Thus the cited art lacks explicit description of the structural features of the invention as required for anticipation under 35 U.S.C. § 102(b). Accordingly, withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Claims 1-2, 4 and 18 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Wu et al. (J. Biol. Chem. 1994, Vol. 269, No. 15, pp. 11542-11546) in view of the

disclosures by Yoshimura et al. (J. Bio. Chem. 1993, Vol. 268, No. 4, pp. 2300-2303), Stanziale et al. Current Molecular Medicine Feb. 2003, Vol. 3, pp. 61-71, especially pages 64-66) and Turturro et al (Blood, 1998, Vol. 92,, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640), for the reasons set forth on page 7 of the Office Action.

Wu et al. is cited as disclosing Hela-S3 cells that can support wild type adenovirus or mutated Ad-dl1312 infection. The Office Action states that Yoshimura et al. discloses an E1a deletion in Ad-dl1312; Stanziale et al. discloses that wild-type adenovirus is considered to be oncolytic and that Hela-S3 is considered to support tumor-specific adenovirus replication in view of the disclosure of Turturro et al.

None of Wu et al., Yoshimura et al. Stanziale et al., or Turturro et al. disclose a recombinant tissue-specific or tumor-specific replication competent adenoviral vectors comprising the E2F promoter operatively linked to an E1a coding region, as presently claimed.

Thus, the cited art lacks explicit description of the structural features of the invention as required for anticipation under 35 U.S.C. § 102(b). Accordingly, withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Rejections under 35 U.S.C. §103

Claims 1-2 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over WO 02/067861A2 and Turturro et al (Blood, 1998, Vol. 92, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640), for the reasons set forth on page 8 of the Office Action.

WO 02/067861A2 is cited as teaching a recombinant adenovirus vector comprising an Adenovirus 5 or 35 backbone wherein the virus comprises a left ITR, a termination signal sequence, an E2F responsive promoter which is operably linked to an E1a gene, an adenoviral packaging signal, and a right ITR. The Office Action states that WO 02/067861A2 does nto teach use of Hela-S3 cells to propagate the virus.

Turturro et al. is cited as teaching that Hela S3 cells express high levels of CAR which make them susceptible to infection by adenovirus. To establish a *prima facie* case of obviousness the prior art reference (or references when combined) must teach or suggest all of the claim

limitations. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. Moreover, when applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Applicants submit that one of skill in the art reading WO 02/067861A2, which is directed to a particular form of recombinant oncolytic adenovirus would not be motivated to combine the reference with Turturro et al. based on the teaching that Hela S3 cells express high levels of CAR. The references provide no motivation to combine the teachings. Absent the present invention as a roadmap, one of skill in the art relying on WO 02/067861A2 would not look to every reference for culturing adenovirus and settle on Turturro et al. Further, Subgroup B and D adenoviruses have been shown to use the CD46 receptor and Ad12 has been shown to infect HeLa cells using the vironectin receptor (Bai et al.).

Absent hindsight, afforded by the claimed invention, one of skill in the art would not combine the cited references. Hence, the rejection under 35 U.S.C. §103(a) is improper and should be withdrawn.

CONCLUSION

In light of the above, Applicants submit that this application is now in condition for allowance and therefore request favorable consideration. If any issues remain which the Examiner feels may be best resolved through a personal or telephonic interview, the Examiner is respectfully requested to contact Applicants' counsel, Linda R. Judge at (415) 836-2586.

Respectfully submitted,

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